REMARKS

The Examiner has withdrawn claims 8, 13-16, 19 and 23-40 from consideration as being drawn to a non-elected invention. As a result, Applicants have canceled these claims without prejudice from the application, but maintain the right to prosecute these claims in a divisional application. With the entrance of this amendment, claims 1-7, 9, 11, 17-18 and 20-22 remain pending in the application.

The Examiner has noted that the present application lacks an Abstract. Submitted herewith on a separate sheet is an abstract in accordance with 37 C.F.R. §1.72(b).

35 U.S.C. Section 112 Rejections

Claims 1-7, 9, 11, 17-18 and 20-22 stand variously rejected under 35 U.S.C. § 112, first paragraph, for not being enabled for vitamin D conjugated to estrogen or its equivalents, and as not being adequately described in the Specification. The relevant inquiry under the enabling provisions of section 112, first ¶, is whether the scope of enablement provided to one of ordinary skill in the art by the disclosure is commensurate with the scope of protection sought by the claims. The gravaman of the examiner's rejection appears to be that the specification lacks working examples relating to estrogens or their equivalents or anti-estrogens.

Applicants would initially note that a specification is not required or mandated to set forth any working examples, let alone working examples for every species to which vitamin D can be conjugated, in order to support the claims. Although Applicants acknowledge that their illustrated embodiments includes conjugation of vitamin D to bisphosphonates, it is clear that it is improper to demand that the claims should be limited to meet the guidelines specified for the illustrated embodiments. Applicants submit, therefore, the Examiner is obliged to provide some modicum of evidence as towhy one of ordinary skill would not have

known how to make estrogens, their equivalents or anti-estrogens in accordance with the presently claimed invention without undue experimentation.

As evidence to the contrary, applicants submit herewith a Declaration of Jeffrey W. Driscoll, Ph.D. While the Declaration is deemed self-explanatory, Applicants would emphasize that Dr. Driscoll provides evidence that one skilled in the art could readily practice the full scope of the claimed invention guided by the specification. For the reasons delineated in paragraph 5 (pages 4-9) of Dr. Driscoll's Declaration, Dr. Driscoll concludes the following:

> [F]rom reading the specification alone, or combining the disclosure therein with what was generally known in the art at the time the application was filed, I believe sufficient biochemical information relating to the chemical reactions, the condition by which the reactions take place, and the functional groups that provide suitable linkage between estrogen, antiestrogen, estrogen equivalent structures and other target molecules to vitamin D was provided in, or could be easily extrapolated from, the specification so that the skilled chemist could practice the claimed invention. Moreover, I believe that no undue experimentation would be required by one of ordinary skill in the art to determine which estrogen, anti-estrogens or target molecules will conjugate with vitamin D (Paragraph 5).

More particularly, as set forth in paragraph 5, Dr. Driscoll states "[u]sing the guidance of the bisphosphonate conjugate synthetic schema [as described in the specification and further described in paragraph 5(iv) of Dr. Driscoll's Declaration] and knowledge of these general reactions well known in the art, one of ordinary skill in the art would have known how to conjugate a vitamin D moiety with an estrogen, estrogen equivalent or the other disclosed target molecules to form the claimed conjugates and pharmaceutical compositions as of the filing date of the present application." In other words, there is a high degree of predictability that a vitamin D acyl halide will react with an amino acid group or a hydroxyl group on a target molecule. In view of Dr. Driscoll's sworn Declaration, Applicants respectfully submit that the specification is enabling for conjugates comprising vitamin D conjugated to estrogen

or their equivalents as well as anti-estrogen to make and use the invention commensurate with the claims.

The Examiner also rejected the pharmaceutical composition claims 20-22, contending that the specification fails to provide any *in vivo* data, working examples and guidance with respect to therapeutic effective dosages of the conjugates. In response to this rejection, Applicants respectfully direct the Examiner's attention to page 23, line 9 to page 26, line 2 which provides the necessary guidance with respect to effective dosages and also enables administration and application of the pharmaceutical compositions. More particularly, page 25, lines 3-10 give specific information regarding oral administration of the pharmaceutical compositions. For example, "the daily dosage of compounds according to this invention generally is about 0.025 to about 2.5 nmol/kg, preferably about 0.025 to about 1 nmol/kg" (page 25, lines 4-6). "For treatment of hyperproliferative diseases such as cancers, the enteral dosage of the conjugates of formula (I), is about 1 mmol to about 100 nmol per unit dosage; for bone diseases, about 0.5 nmol to 50 nmol per unit dosage" (page 25, lines 6-10). Parenteral application is described on page 24, lines 21-23, enteral application on page 24, lines 23-27, rectal administration on page 24, lines 28-32 and topical formulations on page 25, lines 1-2. In view of this explicit guidance in the specification, reconsideration and withdrawal of this 112 rejection are respectfully requested.

Claims 1-7, 9, 11, 17-18 and 20-22 have also been rejected under 35 U.S.C. 112, first paragraph, as lacking an adequate written description, i.e., as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner contends that "only six Vitamin D conjugates are provided and all conjugated to bisphosphonate," and that therefore only these conjugates meet the written description requirement. Again, the gravaman of the Examiner's rejection appears to

be that Applicants' illustrated examples only include bisphosphonates. However, all that is required is that the application reasonably convey the claimed subject matter. In view of Dr. Driscoll's Declaration, Applicants respectfully submit that the description adequately supports the claims in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. One of ordinary skill in the art would easily be able to extrapolate and understand the scope of the claimed genus from the description and species provided in the specification. In view of Dr. Driscoll's Declaration, Applicants should not be limited to the disclosed species, as the scope of the claimed genus is fully supported by and could easily be determined from Applicants' specification and examples. "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation." MPEP § 2164.03. Accordingly, reconsideration and withdrawal of the 112 rejection are respectfully requested.

The Examiner also rejected claims 1 and 17-18 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. More particularly, the Examiner contends that "claim 18 is indefinite because the claim as written reads on every compound that has estrogen like activity .... In addition, the phrase has no support in the specification as filed." Applicants direct the Examiner's attention to page 10, lines 8-9 of Applicants' specification, wherein examples of bone-therapeutic agents including "estrogens or their equivalents" are provided. In view of Dr. Driscoll's Declaration establishing that Applicants' specification is enabling for conjugates comprising one vitamin D conjugated to estrogen or their equivalents, and further in view of proper support for the term "estrogens or their

equivalents" being provided in Applicants' specification, reconsideration and withdrawal of the 112 rejection are respectfully requested.

Prior Art Rejections

The Examiner rejected claims 1, 3-4, 7 and 20-22 under 102(e) as being anticipated by U.S. Patent No. 5,602,116 issued to Knutson ("Knutson"). Independent claim 1 recites a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest. Independent claim 20 recites a pharmaceutical composition comprising a conjugate which includes at least one vitamin D moiety associated with at least one target molecule moiety having an affinity for a tissue of interest, and a suitable pharmaceutically acceptable carrier. Applicants state the following in the specification:

> The terms 'associated with' or 'association' are meant to refer to attachment of linkage of one component of the conjugate (e.g. the vitamin D moiety) or vitamin D moiety and connector to another component of the conjugate, e.g., the target molecule or target molecule and connector, via covalent bonding, hydrogen bonding, metallic bonding, van der Waal forces, ionic bonding, coulombic forces, hydrophobic or hydrophilic forces, adsorption or absorption, chelate type association, or any combination thereof" (page 10, line 30 to page 11, line 4).

The Examiner contends that the following passage from the Knutson patent anticipates the claimed invention:

> Also included within the scope of the claims would be administration of effective dosages of the analog of formula (I) [e.g. 1-alpha-OH-vitamin D_2] in conjunction with administration of other hormones or other agents which have been shown to stimulate bone formulation in subjects experiencing or tending toward loss of bone mass or bone mineral contents. Such hormones or other agents may include conjugated estrogens or their equivalents, calcitonin, bisphosphonates, calcium supplements, cobalamin, pertussis toxin and boron (Col. 13, lines 20-26).

Applicants respectfully submit that this passage and the other portions of the Knutson reference upon which the Examiner relies relate to co-administration of the analog of formula

(I) with other hormones or agents. These portions do not teach or suggest the claimed conjugates comprising a vitamin D moiety associated with (i.e., via covalent bonding, hydrogen bonding, metallic bonding, van der Waal forces, ionic bonding, coulombic forces, hydrophobic or hydrophilic forces, adsorption or absorption, chelate type association, or any combination thereof) to a target molecule moiety, or pharmaceutical compositions comprising such conjugates. In other words, the Knutson patent does not teach or suggest attachment or linkage of one component of the conjugate (e.g. the vitamin D moiety) or vitamin D moiety and connector to another component of the conjugate (e.g. the target molecule moiety). Instead, the Knutson patent discloses co-administration of separate, unattached compositions: a vitamin D analog with hormones or other agents. Knutson simply does not teach, suggest or enable attaching or chemically bonding the vitamin D analog with the hormones or other agents. Accordingly, reconsideration and withdrawal of the 102(e) rejection are respectfully requested.

The Examiner also rejected all the pending claims under 35 U.S.C. § 103(a) as being unpatentable over Knutson and Kobayashi et al (Anal Biochem 244(2): 374-83, Jan 1997) ("the Kobayashi article") in view of Bauss (Calcif Tissue Int 59(3); 168-73, Sept 1996, PTO 892) ("the Bauss article"). Applicants respectfully submit that the 103(a) rejection requiring a combination of the Kobayashi and Bauss articles with the Knutson patent is improper pursuant to 35 U.S.C. § 103(c) because the Knutson patent is only available as a reference under section 102(e), and not under section 103(a). Section 103(c) dictates the following:

> Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Applicants submit that the subject matter in the Knutson patent as well as the claimed invention in the present application were, at the time the claimed invention was made, owned

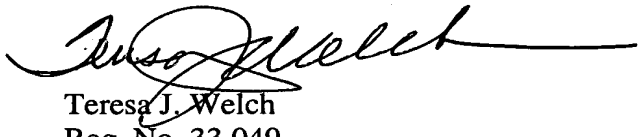
by Bone Care International, Inc. or subject to an obligation of assignment to Bone Care International, Inc. As indicated on the enclosed assignment recordation form pertaining to the Knutson patent, the inventors for the Knutson patent (Joyce C. Knutson, Charles W. Bishop and Richard B. Mazess) assigned their rights to Bone Care International, Inc. on April 3, 1995. The assignment recordation form indicates the assignment was recorded at reel 7498, frame 0210 on April 3, 1995. As indicated on the enclosed assignment recordation form pertaining to the present application, the inventors (Richard B. Mazess and Charles W. Bishop) assigned their rights to Bone Care International, Inc. on October 27, 2000. The assignment recordation form indicates the assignment was recorded at reel 011220, frame 0122 on November 2, 2000. Accordingly, using the Knutson reference to reject the claims under 103(a) is improper as the Examiner has characterized the Knutson patent as a 102(e) reference and it was commonly owned by the assignee of the present application. The Examiner is relying upon the Knutson patent to reject the claims under 103(a). Because Knutson is not available as a reference upon which the Examiner can base the 103 rejection, reconsideration and withdrawal of the 103 rejection are respectfully requested.

In any event, even if the Knutson reference were proper, the Kobayashi and Bauss articles, taken separately or combined, do not cure the deficiency of the Knutson patent. In other words, even if it were permissible to combine these references, the combination thereof does not teach or suggest a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest or a pharmaceutical composition comprising the same. Accordingly, all the pending claims are considered allowable.

CONCLUSION

In view of the foregoing, reconsideration and allowance of all the pending claims are respectfully requested. Applicants request a telephonic interview with the Examiner after the Examiner has had an opportunity to review Applicants' comments, and before the Examiner issues a subsequent Office action. Applicants respectfully request that the Examiner contact the undersigned regarding the interview or if any other questions or issues remain.

Respectfully submitted,



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